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Measurement and Clinical Analysis of The Fourteen Major Plasma Proteins in the Cerebrospinal Fluid

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Contents

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Introducton

Studies of proteins in the cerebrospinal fluid (CSF) had been made mainly with the electrophoretogram of the fractions of prealbumin, albumin and α_1-, α_2-, β-, γ-globulins. There have been a few reports on the quantitative determination of individual proteints in CSF[6)10)11)] This was probably due to the fact that concentration of the proteins in CSF is very low, approximately 1/200 of that in the plasma. Since Kabat's report, several papers on quantitative determination of proteins in CSF began to be published[33)34)] and in recent years various techniques of electrophoresis such as filter-paper, agar-gel and cellulose-acetate -membrane, and disc-electrophoresis with polyacrylamide-gel as the supporting media, have developed.[14)35)55)79)80)83)88)]

On the other hand, an electroimmunodiffusion method (EID) was developed in 1966 by LAURELL[43)], HARTLEY[26)] and MERILL[50)]. This method has made quantitative determination of proteins in CSF, especially IgA possible with a few μl of CSF[37)38)66)89)]. However, study on the various proteins other than IgG has been reported only by SCHULLER et al.[67)68)69)70)] They made a comparison of the concentration of individual proteins in several neurological disorders with its mean value of normal subjects without referring to the ratios of the values of individual proteins. Correlation between IgG and IgA and albumin have been reported by TOURTELLOTTE and TAKASE.[82)90)] In the present study, a quantitative determination was made with EID method on the following 13 plasma proteins in CSF Prealbumin (Pre), albumin (Alb), α_1 antitrypsin (α_1 AT), α_1 acidglycoprotein (α_1 AG), α_1 antichymotrypsin (α_1 X), α_2 macroglobulin (α_2 M), α_2 HS glycoprotein (α_2 HS), ceruloplasmin (Cp), haptoglobin (Hp), hemopexin (Hx), transferrin (Tf), β_1C/β_1A globulin (C3) and IgA. IgG was measured with the single radial immunodiffusion method (RID).[48)93)] These 14 proteins occupy approximately 60% of total protein in CSF.

Besides these proteins, α_1 lipoprotein, β_2 glycoprotein II (C3 proactivator) and β_1 E globulin are measureable, but these proteins occupy only a few percent among the total plasma protein in CSF. IgM, β lipoprotein and fibrinogen[13)42)] in CSF are detectable only in a pathological condition, but when there are no increase of total protein in CSF, they appear only in negligible quantities, so that they were excluded in the present study. there have been some reports on β-trace protein in CSF, but this protein was not included in the present study.[47)58)98)]

Forty-eight patients with various neurological pathology were studied, 21 cases of 48 were selected as the control because of no evidence of increased intracranial pressure nor intracranial hemorrhage, and normal total protein.

In the present study the correlation between albumin and individual proteins in the control group was analyzed, followed by clinical analysis of changes of concentrations of 14 proteins in each case.

Materials and Methods

48 patients with various neurological pathology were selected. All of them showed

negative serologic tests for syphilus, and normal rountine biochemical tests. 21 of 45 cases whose total proteins were in normal range were chosen as control. These patients had not received ^{60}Co irradiation or steroid therapy, and history of trauma and signs of intracranial hemorrhage, or liver disease were not obtained. The control group consisted of 17 males and 4 females, the mean age being 40 (ranging from17 to 67).

The CSF was obtained by lumbar puncture or spinal drainage. After centrifuging the fluid, the supernatant was put into a sample tube, and was kept in a freezer at −20°C. Whenever erythrocytes were observed in the sediment, it was discarded. The RID method was used for the measurement of IgG only, and the other 13 proteins were measured by the EID method. Table 2 shows the features of the 14 proteins.[85]

Eletroimmunodiffusion (EID)

1. The specific antiserum-contained agarose plates and electrophoretic conditions.

Using the veronal buffer (pH 8.6, ionic strength $\mu=0.05$), an antibody-containing agarose solution was prepared by mixing a mono-specific antisera with designated volume of 1.5% agarose at 50-55°C (Table 1). A 1.5mm gel was prepared on a large glass plate (205 × 10×1.5mm) by pouring a 28-30ml antibody-containing agarose into a mould made of two glass plates and a U-shaped frame. After congelation (accelerated at 5°C for 5-10 minutes) the upper glass plate was removed gently by sliding it off. After congelating of agarose the wells were punched out with a gel puncher using the template, and, with applying an electric current of 70-100V (corresponding to 2V/cm in the gel), the CSF and standard sera were put into wells one by one. After applicating all samples the electrophoresis was continued with high voltage 280-300V corresponding to 8-10V/cm in the gel for 2-4 hours. For cooling (15-20°C), an elecrophoretic apparatus made by JOHANSSON et al.[32] was used. Table 1 shows concentrations of antisera for each protein on the agarose plate, diameters of wells, volume of CSF, the duration of elecrophoresis, batch numbers of standard sera and their concentrations, rates of dilution, and lower limits of measurement. Antisera and standard sera used in this measurement were manufactured by Behringwerke AG.

2. Staining and mesurement

After electrophoresis was finished the gel plate was immediately immersed in normal saline solution, rinsed in distilled water in 24 hours, dried and strained with coomassie brilliant blue (Fig. 1).

Since the distance from the rocket-shaped base to the top was in proportion to the concentration of each protein, the concentration of the individual proteins in CSF could be determined.

Single radial immunodiffusion (RID)

An elecrophoretic supporting medium (1.5% agarose solution at 55°C) was mixed with a mono-specific antiserum, anti-IgG (gamma-chain specific) serum and 0.9% NaCl solution (final concentration)[30] in order to prevent elution of euglobulin and pseudoglobulin. In the same way as the EID method, the agar plate of 1.5mm in thickness was prepared,

Table 1. Condition of the electroimmunodiffusion (EID) (IgG was measured with single radial immunodiffusion)

Concentration of antiserum (%)	Pre	1	Alb	2	α_1 AG	0.5	α_1 AT	1	α_1 X	0.5	Cp	0.5	α_2 M	0.5	α_2 HS	1	Hp	0.5	Hx	1	Tf	1	C3	0.5	IgA	0.5	IgG	2
Diameter of hole (mm)		2.5		2		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		3
CSF volume in hole (μl)		5		2		5		5		5		5		5		5		5		5		5		5		5		10
Duration of electrophoresis (hs)		2		2.5		3		3		3		3		4		3		3		3		4		3		1		
Standard serum		P-S B		SHS		P-S B		P-S X		P-S X		P-S P		P-S B		P-S B		P-S B		P-S B		P-S X		P-S B		SHS		SHS
Batch number		No. 472		No. 972		No. 472		No. 572		No. 572		No. 1271		No. 472		No. 472		No. 472		No. 472		No. 572		No. 472		No. 972		No. 972
Concentration (mg dl) (I. U./ml)		10		5650		32		16.5		2 (2.1)		30		60		20		68		29		20		30		260 (155)		1500 (172.5)
Dilution		1 : 100		1 : 500		1 : 200		1 : 80		1 : 20		1 : 200		1 : 400		1 : 100		1 : 400		1 : 200		1 : 100		1 : 100		1 : 1600		1 : 1600
		1 : 50		1 : 250		1 : 100		1 : 40		1 : 10		1 : 100		1 : 200		1 : 50		1 : 200		1 : 100		1 : 50		1 : 50		1 : 800		1 : 800
		1 : 25		1 : 100		1 : 50		1 : 20		1 : 5		1 : 50		1 : 100		1 : 25		1 : 100		1 : 50		1 : 25		1 : 25		1 : 400		1 : 400
Lowest limit of measurement (mg dl)		0.1		2.0		0.1		0.1		0.05		0.04		0.07		0.04		0.04		0.1		0.1		0.08		0.05		0.5

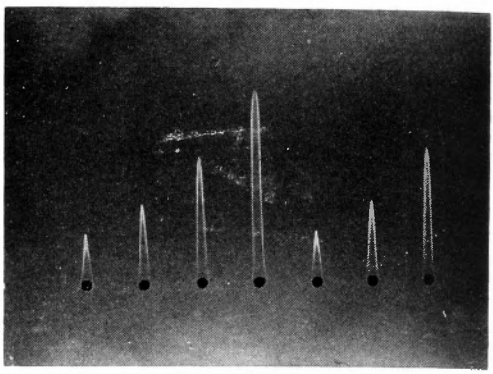

Fig. 1. Electroimmunodiffusion assay of α_1 antitrypsin

and wells of 3 mm in diameter were punched out. After 10 μl of the CSF and diluted standard sera were put into wells, a single diffusion was made for more than 48 hours. Diameters of ring were measured in order of 0.1mm, and IgG concentration of each CSF was determined by the ratio of the area of ring to concentration.

Results

1) The control group

a) Standard concentrations

Table 3 shows the mean value and standard deviation of individual proteins obtained from the measurement of 21 control cases. In several cases concentrations of α_1 X, Cp, α_2 M, α_2 HS, Hp, and Hx were too low to measure. Thus, their concentrations were provisionally recorded as 0 mg/dl in parentheses.

b) Correlation between albumin and individual proteins.

Among proteins measured in 21 control cases, α_1 X and Hx were unmeasurable in one case, and Cp, α_2 M, α_2 HS and Hp in several cases. These were provisionarly regarded as 0 mg/dl, and

Table 2. Human plasma proteins

(guoted from Y. Terano Immunologibal determination of human plasma proteins)

abbreviated word	Plasma protein	M. W.	standard value (mg dl)	fraction and another name
Pre	prealbumin	6, 1000	20±8	thyroxin binding prealbumin
Alb	albumin	6, 9000	4100±600	
α_1AG	α_1 acidglycoprotein	44, 100	60±20	α_1, orosomucoid α_1
α_1AT	α_1 antitrypsin	54, 000	295±74	α_1, α_1-trypsin inhibitor
α_1X	α_1 antichymotrypsin	69, 000	48. 7±6. 5	α_1, α_1 X-glycoprotein α_1 antichymotrypsin
α_2HS	α_2 HS-glycoprotein	49, 000	50±20	α_2, α_2 HS-mucoid Ba-α_2-glycoprotein
Cp	ceruloplasmin	160, 000	35±10	α_2,
α_2M	α_2 macroglobulin	820, 000	f 290+74 m 240+60	α_2, α_2-antiplasmin
Hp	haptoglobin	85, 000 (1-1)	100±50	α_2, α_2-seromucoid
Hx	hemopexin	80, 000	50±10	β_1, β_1 B-globulin
Tf	transferrin	90, 000	250±40	β_1, siderophilin
β_1C (C3)	β_1 C-globulin	240, 000	100±30	C3 component β_1, change to β_1A
IgA	immunoglobulin A	170, 000	210±80	β_2, γA, β_2A, γ_1A, βX
IgG	immunoglobulin G	150, 000	1300±500	γ, γG-globulin

mean of mobility

Alb	0. 0	Tf	100. 0	Pre	−42. 21	α_1 AG	9. 60	α_1AT	22. 35
α_1X	38. 25	α_2HS	57. 57	Cp	59. 65	α_2M	63. 10	Hp 1-1	56. 61
Hp 2-1	64. 07	Hp 2-2	73. 17	Hx type 1	90. 00	Hx type 2	101. 00	β_1C	114. 82
β_1A	87. 44	TfII	120. 00	IgA	127. 84	IgG	169. 47		

Table 3. The concentration of proteins in CSF and plasma (mg/dl) These proteins were measured with EID method in 21 controls,except IgG which was measured with single radial immunodiffuion.
corrected velues are shown in brackets, Details are in the text.

	C S F				plasma	
	Terano	S. D.	Bock	Schuller	Bock	Matsuba
Pre	1. 26	0. 58	1. 73		28	20
Alb	18. 4	7. 7	17. 5	17. 5	3660	4100
α_1 AG	0. 35	0. 28	0. 41	0. 45	104	60
α_1 AT	0. 98	0. 52	0. 81	1. 11	185	295
α_1 X	0. 18 (0. 16)	0. 10	0. 49 a. u.		106 a. u.	48. 7
Cp	0. 13 (0. 10)	0. 07	0. 06	0. 22	31	35
α_2M	0. 24 (0. 19)	0. 15	0. 08	0. 2	241	260
α_2HS	0. 25 (0. 20)	0. 12	0. 17	0. 16	43	50
Hp	0. 18 (0. 15)	0. 16	0. 21	0. 12	235	100
Hx	0. 37 (0. 35)	0. 17	0. 30	0. 26	80	50
Tf	1. 67	0. 76	1. 45	1. 81	230	250
C3	0. 19	0. 13	0. 15	0. 25	74	100
IgA	0. 24	0. 20	0. 16	0. 35	150	210
IgG	3. 43	1. 69	2. 45	2. 70	1040	1300

Table 4. Relationship between albumin and individual proteins in CSF of 21 controls. (r correlation coefficient, Y=a+bX : regression line, X and Y mean the concentration of albumin and each protein, # the unmeasured value was regarded as 0 mg/dl

	r	a	b
Pre	0.682	0.919	0.030
α_1 AG	0.776	0.033	0.018
α_1 AT	0.888	−0.078	0.063
# α_1 X	0.700	−0.041	0.010
# Cp	0.618	−0.040	0.005
# α_2 M	0.631	−0.069	0.015
# α_2 HS	0.690	−0.055	0.014
# Hp	0.373	−0.014	0.007
Hx	0.788	0.019	0.019
Tf	0.925	−0.162	0.102
C3	0.789	0.005	0.010
IgA	0.708	−0.035	0.015
IgG	0.878	−0.307	0.204

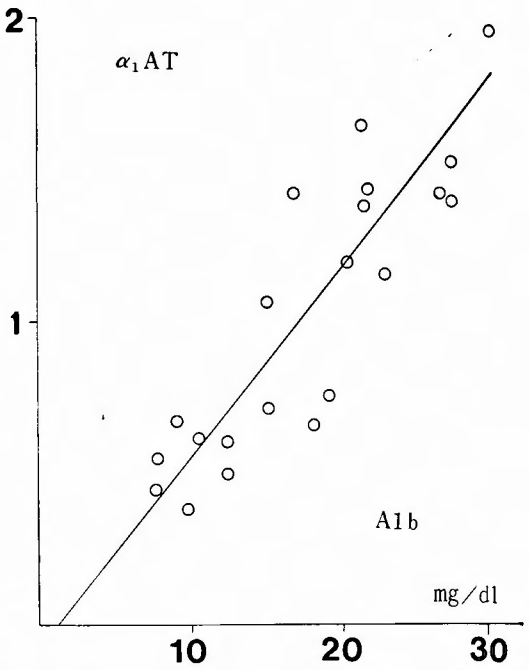

Fig. 2. Correlation between albumin and α_1 antitrypsin in CSF (Regression line: Y=0.063X−0.078, correlation coefficient r=0.888)

their respective correlations are shown in Table 4. The relation between α_1 AT and albumin is shown in Fig. 2. Their correlation coefficient was high, and both α_1 AT and albumin were proved to change in parallel when their concentrations in CSF were within the normal range. No correlation was observed only in Hp. The correlation between Alb and Cp as well as α_2 M was low, and the correlation between Alb and Pre was extremely low, though Pre was measurable in all cases. Whereas the correlation between Alb and Tf as well as IgG was considerably high.

2) Percentages of concentrations of individual proteins

a) Comparative study in intracranial tumors and various neurological diseases

An increase or decrease of each protein was compared in terms of the percentages of concentrations. The absolute values (mg/dl) were used only when total of 14 proteins were shown. As shown in table 5a, the changes in concentration of Pre were negligible, but when total of 14 proteins was high, the percentage of its concentration was low, and reversely when total of 14 proteins was low, the percentage of its concentration was high. As shown in Table 6, in cases of ruptured aneurysm, α_1 AG, α_1 AT, α_1 X, α_2 M and Hx increased, while Tf decreased. On the other hand, in cases of glioma, Hx and Tf showed a slight increase, while IgG showed a tendency to decrease.

However, in cases of pituitary adenoma, the concentration was almost the same as that of the control. In cases of neurinoma, Cp and C3 increased moderately, and Hp, IgA and

Table 5a. The concentration of the 14 proteins (the upper row) and the percentage of individual proteins to total of 14 proteins (the lower row).

	No. ①	No. ②	No. ③	No. ④	No. ⑤	No. 6	No. ⑦	No. ⑧
Pre	0.97	0.90	1.23	1.43	1.12	2.00	1.40	1.21
Alb	21.8	23.1	18.0	9.10	18.2	14.3	19.6	20.3
α_1 AG	0.46	0.31	0.58	0.26	0.52	0.34	0.31	0.65
α_1 AT	1.13	1.20	1.15	0.66	1.20	1.10	0.80	1.30
α_1 X	0.20	0.20	0.29	0.07	0.11	0.16	0.16	0.29
Cp	0.07	0.12	0.06	—	0.10	—	0.12	0.06
α_2 M	0.32	0.32	0.23	0.07	0.27	0.15	0.15	0.20
α_2 HS	0.38	0.28	0.28	—	—	0.04	0.34	0.15
Hp	0.44	0.04	0.27	0.10	0.17	—	—	0.22
Hx	0.45	0.40	0.40	0.27	0.70	0.42	0.39	0.40
Tf	1.98	2.31	1.74	0.60	1.85	1.58	1.74	1.98
β_1C/β_1A	0.33	0.35	0.25	0.10	0.35	0.12	0.10	0.21
IgA	0.21	0.40	0.32	0.17	0.17	—	—	0.42
IgG	2.90	2.70	3.34	1.40	4.20	1.73	2.50	2.10
total	31.64	32.63	28.10	14.23	28.96	21.94	27.61	29.46
%								
Pre	3.07	2.76	4.38	10.1	3.87	9.12	5.07	4.11
Alb	68.9	70.8	64.1	63.9	62.8	65.2	71.0	68.9
α_1 AG	1.45	0.95	2.06	1.83	1.80	1.55	1.12	2.21
α_1 AT	3.57	3.68	4.09	4.64	4.14	5.01	2.90	4.41
α_1 X	0.63	0.61	1.03	0.49	0.38	0.73	0.58	0.98
Cp	0.22	0.37	0.21	—	0.34	—	0.43	0.20
α_2 M	1.01	0.98	0.82	0.49	0.93	0.68	0.54	0.68
α_2 HS	1.20	0.86	1.00	—	—	0.18	1.23	0.51
Hp	1.39	0.12	0.96	0.70	0.59	—	—	0.74
Hx	1.42	1.23	1.42	1.90	2.42	1.91	1.41	1.36
Tf	6.26	7.08	6.19	4.22	6.39	7.20	6.30	6.72
β_1C β_1A	1.04	1.07	0.88	0.70	1.21	0.54	0.36	0.71
IgA	0.66	1.23	1.14	1.19	0.59	—	—	1.42
IgG	9.17	8.27	11.89	9.84	14.5	7.89	9.05	7.13

	No. ⑨	No. ⑩	No. ⑪	No. ⑫	No. ⑬	No. ⑭	No. ⑮	No. ⑯
Pre	1.79	1.44	1.07	1.75	1.43	1.70	1.54	1.51
Alb	36.0	18.8	18.8	19.0	11.4	27.4	21.4	18.0
α_1 AG	1.29	0.24	0.52	0.36	0.39	0.58	0.34	0.34
α_1 AT	2.86	1.10	1.10	0.75	0.44	1.53	1.38	0.65
α_1 X	0.38	0.20	0.15	0.11	0.05	0.38	0.20	0.36
CP	0.32	0.12	0.09	—	0.02	0.18	0.12	0.15
α_2 M	0.44	0.38	0.20	0.11	0.07	0.65	0.51	0.33
α_2 HS	0.48	0.08	—	0.28	—	0.27	0.48	0.15
Hp	0.60	—	0.30	0.20	0.07	0.39	—	0.43
Hx	0.68	0.37	0.34	0.29	—	0.52	0.40	0.29
Tf	3.01	1.64	1.70	1.50	0.99	2.42	2.18	2.24
β_1C β_1A	0.55	0.21	0.21	0.10	0.10	0.37	0.21	0.30
IgA	0.88	0.23	0.26	0.17	0.08	0.65	0.18	0.33
IgG	6.53	3.75	2.90	3.75	1.88	5.40	4.20	3.97
T. P	55.81	28.51	27.64	28.37	16.92	42.44	33.24	29.08
%								
Pre	3.21	5.05	3.87	6.17	8.45	4.01	4.54	5.19
Alb	64.50	65.9	68.0	67.0	67.4	64.6	64.4	61.9
α_1 AG	2.31	0.84	1.88	1.27	2.30	1.37	1.02	1.17
α_1 AT	5.12	3.86	3.98	2.64	2.60	3.61	4.15	2.24
α_1 X	0.68	0.70	0.54	0.39	0.30	0.90	0.60	1.24
Cp	0.57	0.42	0.33	—	0.12	0.42	0.36	0.52
α_2 M	0.79	1.33	0.72	0.38	0.41	1.53	1.53	1.13
α_2 HS	0.86	0.28	—	0.99	—	0.64	1.44	0.52
Hp	1.08	—	1.09	0.70	0.41	0.92	—	1.48
Hx	1.22	1.30	1.23	1.02	—	1.23	1.20	1.00
Tf	5.39	5.75	6.15	5.29	5.85	5.70	6.56	7.70
β_1C/β_1A	0.99	0.74	0.76	0.35	0.59	0.87	0.63	1.03
IgA	1.58	0.81	0.94	0.60	0.47	1.53	0.54	1.13
IgG	11.70	13.15	10.49	13.22	11.11	12.72	12.63	13.65

	No. ⑰	No. ⑱	No. ⑲	No. ⑳	No. ㉑	No. ㉒	No. ㉓	No. ㉔
Pre	1.70	1.59	1.87	1.54	2.16	1.67	1.58	1.66
Alb	26.6	20.3	30.0	54.0	57.0	22.7	12.4	15.0
α_1 AG	0.40	0.55	0.52	1.37	1.60	0.48	0.16	0.18
α_1 AT	1.42	1.20	1.97	3.87	3.90	1.15	0.60	0.71
α_1 X	0.16	0.16	0.16	0.49	0.49	0.16	—	0.07
Cp	0.12	0.08	0.10	0.46	0.42	0.09	—	—
α_2 M	0.29	0.23	0.15	0.88	0.95	0.27	0.07	0.07
α_2 HS	0.18	0.37	0.30	0.82	0.92	0.28	0.25	—
Hp	0.09	0.17	0.10	1.65	2.70	0.07	—	0.04
Hx	0.40	0.37	0.70	0.50	0.60	0.34	0.17	0.19
Tf	3.07	1.75	2.51	4.00	4.10	2.76	1.04	1.49
β_1C/β_1A	0.35	0.20	0.23	0.95	0.96	0.20	0.06	0.10
IgA	0.17	0.37	0.27	1.59	1.15	0.42	0.05	0.17
IgG	5.80	5.30	3.75	15.5	11.1	4.20	1.73	2.70
total	40.75	32.64	42.63	87.62	85.75	34.79	18.11	22.38
%								
Pre	4.17	4.87	4.39	1.75	2.52	4.80	8.72	7.42
Alb	65.3	62.2	70.4	60.5	66.5	65.2	68.5	67.0
α_1 AG	0.98	1.69	1.22	1.56	1.87	1.38	0.88	0.80
α_1 AT	3.48	3.68	4.62	4.42	4.55	3.31	3.13	3.17
α_1 X	0.39	0.49	0.38	0.56	0.57	0.46	—	0.31
Cp	0.29	0.24	0.23	0.52	0.49	0.26	—	—
α_2 M	0.71	0.70	0.35	1.00	1.11	0.78	0.39	0.31
α_2 HS	0.44	1.13	0.70	0.94	1.07	0.80	1.38	—
Hp	0.22	0.52	0.23	1.88	3.15	0.20	—	0.18
Hx	0.98	1.13	1.64	0.57	0.70	0.98	0.94	0.85
Tf	7.53	5.36	5.89	4.56	4.15	7.93	5.74	6.66
β_1C/β_1A	0.86	0.61	0.54	1.08	1.12	0.57	0.33	0.45
IgA	0.42	1.13	0.70	1.81	1.34	1.21	0.28	0.76
IgG	14.23	16.24	8.80	17.69	12.90	12.07	9.55	12.06

	No. ㉕	No. ㉖	No. ㉗	No. ㉘	No. ㉙	No. ㉚	No. ㉛	No. ㉜
Pre	0.81	1.30	0.97	1.10	1.46	0.73	1.47	1.50
Alb	7.60	13.7	10.0	10.8	12.4	8.10	12.5	14.6
α_1 AG	0.20	0.17	0.17	0.16	0.18	0.26	0.34	0.24
α_1 AT	0.44	0.71	0.38	0.62	0.49	0.55	0.98	0.77
α_1 X	—	0.07	0.05	0.07	0.07	0.05	0.13	0.11
Cp	—	0.04	—	—	—	0.06	0.06	—
α_2 M	—	—	—	0.15	—	0.15	0.24	0.29
α_2 HS	—	0.34	0.14	—	—	0.11	0.18	0.09
Hp	—	—	—	0.04	0.04	—	0.09	0.09
Hx	0.12	0.21	0.29	0.24	0.29	0.18	0.42	0.25
Tf	0.46	0.67	0.71	1.08	1.38	0.53	1.76	1.64
β_1C β_1A	0.08	—	0.15	0.15	0.15	0.08	0.14	0.14
IgA	0.05	0.17	0.17	0.12	0.08	0.09	0.18	0.14
IgG	1.57	1.70	1.62	2.00	1.55	1.34	2.05	2.50
total	11.33	19.07	14.70	17.05	18.09	12.23	20.54	22.36
%								
pre	7.15	6.82	6.60	9.40	8.07	5.97	7.16	6.71
Alb	67.1	71.8	68.0	63.4	68.5	66.2	60.9	65.3
α_1 AG	1.77	0.89	1.16	0.94	1.00	2.13	1.66	1.07
α_1 AT	3.88	3.72	2.59	3.64	2.71	4.50	4.77	3.44
α_1 X	—	0.37	0.34	0.41	0.39	0.41	0.63	0.49
Cp	—	0.21	—	—	—	0.49	0.29	—
α_2 M	—	—	—	0.88	—	1.23	1.17	1.30
α_2 HS	—	1.78	0.95	—	—	0.90	0.88	0.40
Hp	—	—	—	0.23	0.22	—	0.44	0.40
Hx	1.06	1.10	1.97	1.41	1.60	1.47	2.04	1.12
Tf	4.06	3.51	4.83	6.34	7.63	4.33	8.57	7.33
β_1C β_1A	0.71	—	1.02	0.88	0.83	0.65	0.68	0.63
IgA	0.44	0.89	1.16	0.70	0.44	0.74	0.88	0.63
IgG	13.86	8.91	11.02	11.74	8.57	10.96	9.98	11.18

	No. ㉝	No. ㉞	No. ㉟	No. ㊱	No. ㊲	No. ㊳	No. ㊴	No. ㊵
Pre	1.62	1.82	1.50	0.95	1.92	1.36	1.70	1.18
Alb	23.0	9.90	15.4	6.50	15.9	12.9	27.4	11.2
α_1 AG	0.42	0.28	0.24	0.16	0.78	0.28	0.58	0.24
α_1 AT	0.80	0.77	0.65	0.44	1.26	0.55	1.70	0.65
α_1 X	0.20	0.20	0.11	0.11	0.24	0.11	0.24	0.11
Cp	0.08	—	0.06	—	0.12	0.06	—	0.06
α_2 M	0.36	0.15	0.24	0.15	0.29	0.38	0.24	0.24
α_2 HS	0.25	0.15	—	—	0.71	—	0.31	0.18
Hp	—	—	0.05	—	0.13	0.22	0.05	—
Hx	0.24	0.34	0.14	0.42	0.55	0.21	0.57	0.15
Tf	1.74	1.09	1.43	0.43	0.99	1.37	2.41	1.09
β_1C/β_1A	0.15	0.14	0.14	0.08	0.17	0.21	0.26	0.14
IgA	0.05	0.09	0.05	—	0.18	0.14	0.42	—
IgG	2.71	1.36	2.90	1.03	2.90	1.84	5.80	2.05
total	28.91	16.30	22.81	10.27	26.14	19.63	41.68	17.29
%								
Pre	5.61	11.17	6.58	9.25	7.34	6.93	4.08	6.82
Alb	70.3	60.7	67.5	63.3	60.8	65.7	65.7	64.8
α_1 AG	1.46	1.72	1.05	1.56	2.98	1.43	1.39	1.39
α_1 AT	2.77	4.72	2.84	4.28	4.82	2.80	4.08	3.76
α_1 X	0.69	1.23	0.48	1.07	0.92	0.56	0.58	0.64
Cp	0.28	—	0.26	—	0.46	0.31	—	0.34
α_2 M	1.24	0.92	1.05	1.46	1.11	1.94	0.58	1.39
α_2 HS	0.87	0.92	—	—	2.72	—	0.74	1.04
Hp	—	—	0.22	—	0.50	1.12	0.12	—
Hx	0.83	2.09	0.61	4.09	2.10	1.07	1.37	0.87
Tf	6.03	6.69	6.27	4.19	3.79	6.98	5.78	6.30
β_1C/β_1A	0.52	0.86	0.61	0.78	0.65	1.07	0.62	0.81
IgA	0.17	0.55	0.22	—	0.69	0.71	1.01	—
IgG	9.39	8.34	12.71	10.03	11.09	9.37	13.92	11.86

	No. ㊶	No. ㊷	No. ㊸	No. ㊹	No. ㊺	No. ㊻	No. ㊼	No. ㊽
Pre	1.43	1.33	1.43	1.84	1.43	1.82	1.18	1.40
Alb	21.8	16.7	45.0	45.2	13.3	19.7	21.1	14.9
α_1 AG	0.49	0.65	0.87	1.56	0.23	0.48	0.49	0.24
α_1 AT	1.45	1.42	3.62	3.78	0.68	1.10	1.64	1.06
α_1 X	0.16	0.20	0.33	0.77	0.07	0.20	0.24	0.13
Cp	0.08	—	0.25	0.45	0.04	—	0.12	0.07
α_2 M	0.15	0.20	0.32	0.64	0.11	0.24	0.24	0.20
α_2 HS	0.25	0.18	0.68	0.29	—	0.08	0.18	0.18
Hp	0.24	0.09	0.17	1.56	0.07	0.09	—	0.17
Hx	0.75	0.34	0.50	0.57	0.27	0.42	0.34	0.37
Tf	1.88	1.76	3.21	2.96	1.24	1.52	1.80	1.21
β_1C/β_1A	0.20	0.17	0.70	1.10	0.15	0.17	0.21	0.14
IgA	0.28	0.28	0.61	1.60	—	0.37	0.28	0.18
IgG	5.50	2.90	12.6	12.1	1.74	6.30	3.08	2.05
total	34.66	26.22	70.29	74.42	19.00	32.49	30.90	22.30
%								
Pre	4.13	5.07	2.03	2.47	7.53	5.60	3.82	6.28
Alb	62.9	63.7	64.0	60.7	70.00	6.06	68.3	66.8
α_1 AG	1.41	2.48	1.24	2.10	1.21	1.48	1.59	1.08
α_1 AT	4.18	5.42	5.15	5.08	3.58	3.39	5.31	4.75
α_1 X	0.46	0.76	0.47	1.03	0.37	0.62	0.78	0.58
Cp	0.23	—	0.36	0.60	0.21	—	0.39	0.31
α_2 M	0.43	0.76	0.46	0.86	0.58	0.74	0.78	0.90
α_2 HS	0.72	0.69	0.97	0.39	—	0.24	0.58	0.81
Hp	0.69	0.34	0.24	2.10	0.37	0.28	—	0.76
Hx	2.16	1.30	0.71	0.77	1.42	1.29	1.10	1.66
Tf	5.42	6.71	4.57	3.98	6.53	4.68	5.83	5.43
β_1C/β_1A	0.58	0.64	1.00	1.48	0.79	0.52	0.68	0.63
IgA	0.81	1.07	0.87	2.15	—	1.14	0.91	0.81
IgG	15.9	11.1	17.93	16.3	9.16	19.4	9.97	9.19

Table 5b. Clinical diagnosis of 48 cases (♯ : control group)

	No. 1	Y. M.	11	m	cerebellar medulloblastoma, postop.
	No. 2	M. C.	14	f	cerebellar medulloblastoma, postop.
	No. 3	S. R.	27	f	third ventricle tumor, postop.
♯	No. 4	W. T.	22	m	lateral ventricle ependymoma
	No. 5	S. T.	40	m	glioblastoma., postop. epilepsy
	No. 6	S.M.	35	m	recurrence of astrocytoma, grade 3, epilepsy
	No. 7	N. M.	1	f	optic glioma
	No. 8	S. H.	34	m	osteoma of mastoid, postop., spinal drainage
	No. 9	M. H.	53	f	maetastasis (adenocarcinoma)
	No. 10	N. M.	13	m	pinealoma. postop.
	No. 11	H. B.	42	m	meningioma (sphenoidal ridge), postop.
♯	No. 12	K.K.	35	m	pituitary adenoma
	No. 13	M. M.	21	f	pituitary adenoma,elevation of RAT, LDH
♯	No. 14	S. H.	19	m	pituitary adenoma
♯	No. 15	I. T.	46	m	pituitary adenoma
♯	No. 16	M. H.	43	f	pituitary adenoma, malignant
♯	No. 17	N. Y.	44	m	acromegaly, diabetes m.
♯	No. 18	O. E.	48	f	meningioma of tuberculum sella, mitosis +
♯	No. 19	M. K.	38	f	meningioma of tuberculum sella
	No. 20	K. S.	52	f	acoustic neurinoma
	No. 21	D. M.	37	m	trigeminal neurinoma
♯	No. 22	S. N.	47	m	craniopharyngioma
♯	No. 23	K. K.	25	f	epilepsy
♯	No. 24	I. S.	23	m	epilepsy
♯	No. 25	N. S.	25	f	epilepsy
	No. 26	T. K.	27	f	ventricle dilatation, after head injury
♯	No. 27	H. K.	17	f	hysteria
	No. 28	T. H.	56	m	enlargement of septum pellucidum.
♯	No. 29	S. J.	52	m	optic neuritis
♯	No. 30	K. J.	25	m	hypochondriasis
	No. 31	T. Y.	61	f	gait disturbance
	No. 32	K. Y.	31	f	traumatic cervical syndrome
	No. 33	O. H.	20	m	chronic subdural hematoma
	No. 34	N. M.	27	f	head injury type, Ⅲ (Araki)
	No. 35	I. H.	45	m	head injury type, Ⅰ (Araki)
	No. 36	O. T.	46	f	ruptured aneurysm, NPH
♯	No. 37	K. M.	57	f	ruptured aneurysm, NPH
	No. 38	W. H.	25	m	arterio-venous malformation
♯	No. 39	M. L.	43	m	vertebral thrombosis
	No. 40	H. M.	7	f	verterbral stenosis
♯	No. 41	H. K.	67	m	parkinsonism
♯	No. 42	M. G.	42	m	spasmodic torticollis
	No. 43	K. K.	26	m	multiple screlosis
	No. 44	T. Y.	24	m	meningitis
	No. 45	N. G.	5	m	hydrocephlus
	No. 46	M. H.	6	m	Arnold-Chiari malformation, hydrocephalus
♯	No. 47	U. K.	61	m	cervical spondylosis
♯	No. 48	T. Y.	27	m	cervical strain syndrome

Table 6. Change of plasma proteins in CSF of brain tumors and various nenrological disorders. (%) (Brackets show estimate in the cases which a content of the protein was unmeasurable. For reference CSF in hydrocephalus was obtained from the ventricle.)

	control	glioma	pituit. adenoma	mening-ioma	neurin-oma	epilepsy	head inj.	Aneur-ysm	miscella-neous	hydroce-phalus
No. of cases	(21)	(6)	(5)	(2)	(2)	(3)	(3)	(2)	(5)	(3)
Pre	4.65	4.79	4.74	4.60	2.00	7.31	7.25	7.88	7.36	10.88
Alb	66.5	66.1	63.5	66.8	64.7	63.2	66.8	61.5	66.8	60.7
α_1 AG	1.27	1.54	1.20	1.42	1.60	0.98	1.37	2.58	1.14	1.36
α_1 AT	3.56	4.03	3.22	4.21	4.19	3.16	3.25	4.67	3.34	3.21
α_1 X	0.59	0.64	0.53	0.43	0.53	(0.38)	0.74	0.97	0.38	0.94
Cp	0.35	(0.23)	0.32	0.24	0.47	(0.22)	(0.26)	(0.25)	0.30	0.58
α_2 M	0.70	0.85	0.95	0.50	0.99	(0.38)	1.10	1.21	0.91	2.18
α_2 HS	0.72	(0.62)	0.88	0.89	0.94	(0.70)	(0.66)	(1.38)	1.20	0.73
Hp	0.55	0.77	0.55	0.36	1.81	(0.22)	(0.22)	(0.27)	0.24	(0.99)
Hx	1.28	1.65	1.17	1.42	0.59	0.87	1.05	2.66	1.45	1.32
Tf	6.05	6.30	5.81	5.66	4.08	5.40	6.24	4.45	5.31	7.84
C3	0.69	0.94	0.66	0.57	1.03	0.43	0.63	0.69	0.81	1.05
IgA	0.88	0.95	0.73	0.85	1.48	0.49	0.28	(0.37)	0.76	(0.10)
IgG	12.4	10.2	12.3	12.0	15.6	10.8	10.2	10.8	10.0	8.21
Total (mg/dl)	27.69	26.68	34.28	37.64	92.73	18.46	22.77	18.20	16.46	19.12

IgG increased markedly.

In two cases of neurinoma and each case of multiple sclerosis, meningitis and metastatic tumor, abnormality of the CSF protein fraction was extraordinary.

Only in these 5 cases total of 14 proteins increased moderately, but in other cases total protein in CSF remainded within the normal range. In cases of epilepsy, a decrease or IgA and Hp was remarkable.

b) Changes of individual proteins in each case

(1) albumin (Alb)

In the lower part of Table 5a the percentage of Alb to total of 14 proteins were shown.

The percentage of Alb was 60 to 70 %, but when a ratio of the plasma Alb to total plasma protein was high, the percentage of Alb in CSF also increased relatively. Consequently there is highly significant correlation between Alb in CSF and that in plasma.

(2) Prealbumin (Pre)

A correlation between Pre and Alb was low. (Table 4) Because of no remarkable change of Pre, the measured values were compared with a mean value of the control group.

Pre increased in cases with recurrent astrocytoma, normal pressure hydrocephalus (NPH), and trigeminal neurinoma.

Its remarkable increase was also observed in the ventricular fluid in case of congenital communicating hydrocephalus.

A decrease of Pre was observed in glioma.

Table 7. Increase of α_1 AG, α_1 AT, and/or α_1 X
(Brackets show the corrected value in the case with incresed plasma albumin)

Case	α_1 AG	α_1 AT	α_1 X	
	1.27%	3.95%	0.69%	Control
No. 9	2.21(2.04)	4.41(4.07)	0.98(0.90)	Metastasis
No. 13	2.30	2.60	0.30	Pituitary adenoma
No. 16	1.17	2.24	1.24	Pituitary adenoma
No. 33	1.72	3.25	0.81	Chr. sub. hematoma
No. 34	1.72(1.59)	4.72(4.36)	1.23(1.14)	Head inj. type Ⅲ
No. 36	1.56	4.28	1.07	Aneurysm, 2 m. after rupture
No. 37	2.98(2.58)	4.28(4.18)	0.92(0.80)	Aneurysm, NPH
No. 42	2.48(2.02)	5.42(4.42)	0.76(0.62)	Torticollis
No. 44	2.10(1.86)	5.08(4.51)	1.03(0.91)	Meningitis
No. 47	1.59(1.55)	5.31(5.20)	0.78(0.76)	Cervical spondylosis

Table 8. Change of ceruloplasmin and transferrin

	Cp	Tf	
	0.24%	6.30%	control
No. 4	—	4.22	ependymoma
No. 6	—	7.20	astrocytoma
No. 7	0.43	6.30	optic glioma
No. 9	0.57	5.39	metastasis
No. 10	0.42	5.73	pinealoma
No. 12	—	5.29	pituitary adenoma
No. 13	0.12	5.85	pituitary adenoma
No. 16	0.52	7.70	pituitary adenoma, malignant
No. 17	0.29	7.53	acromegaly
No. 20	1.00	4.56	acoustic neurinoma
No. 21	1.11	4.15	trigeminal neurinoma
No. 22	0.26	7.93	craniopharyngioma
No. 23	—	5.74	epilepsy
No. 24	—	6.66	epilepsy
No. 25	—	4.06	epilepsy
No. 29	—	7.63	optic neuritis
No. 31	0.29	8.57	gait disturbance
No. 32	—	7.33	traumatic cervical syndrom
No. 34	—	6.69	head injury type Ⅲ (Araki)
No. 37	0.46	3.79	aneurysm, NPH
No. 39	—	5.78	vertebral thrombosis
No. 42	—	6.71	spasmodic torticollis
No. 44	0.60	3.98	menigitis
No. 45	0.21	6.53	hydrocephalus, atrophy
No. 46	—	4.68	Arnold-Chiari, cystic

(3) α_1 acidglycoprotein (α_1 AG)

As shown in Table 5a and Table 7, α_1 AG increased in cases with metastatic tumor, ruptured aneurysm, meningitis and spasmodic torticollis, and in one case of pituitary adenoma. A slight increase was observed in cases of glioma, meningitis and acromegaly.

(4) α_1 antitrypsin (α_1 AT)

As shown in Table 7, α_1 AT increased in cases of metastasis, head injury (type 3), meningitis, NPH and cervical spondylosis. In these cases, concentration of Alb in the plasma showed a decrease. Thus corrected values were close to those of the control, as shown in the parentheses. In cases of metastasis, α_1 AT did not always show a increase specifically. On the other hand α_1 AT decreased in pituitary adenoma and chronic subdural hematoma.

(5) α_1 antichymotrypsin (α_1 X)

α_1 X increased in cases of metastasis, head injury (type 3), malignant pituitary adenoma, ruptured aneurysm and meningitis (Table 7). In almost all cases α_1 AT and α_1 X showed a high correlation, but in cases of malignant tumor, only α_1 X increased remarkably.

(6) ceruloplasmin (Cp)

An increase of Cp was observed in cases of metastasis, meningitis, and neurinoma, but in all these cases concentration of Alb was over 30mg/dl and total proteins showed a remarkable increase (Table 8). An increase of Cp was also found in cases of malignant pituitary adenoma. On the other hand a decrease of Cp was observed in cases of spasmodic torticollis. Some other cases showed a decrease of Cp, but in most of these cases total protein was low. Since Cp is a high-molecular protein, its decrease is not always interpreted as significant. Therefore in this study its decrease was regarded as normal.

Table 9. Change of α_2 macroglobulin

Case	Alb	α_2M	
	65%	0.86%	control
No. 1	68.9	1.01	medulloblastoma
No. 2	70.8	0.98	medulloblastoma
No. 3	64.1	0.82	third ventricle tumor
No. 5	62.8	0.93	glioblastoma, cyst +
No. 6	66.8	0.65	Astrocytoma
No. 7	71.0	0.54	optic glioma
No. 10	65.9	1.33	pinealoma
No. 14	64.6	1.53	pituitary adenoma
No. 15	64.4	1.53	pituitary adenoma
No. 33	70.3	1.24	chronic subdural hematoma
No. 34	60.7	0.92	head injury, type Ⅲ
No. 35	67.5	1.05	head injury, type Ⅰ
No. 38	65.9	1.95	arteriovenous malformation

(7) α_2 macroglobulin (α_2 M)

α_2 M is also a very high molecular protein, and was observed in low concentration in many cases. Its correlation with Alb is low (Table 9). α_2 M increased in cases of arteriovenous malformation and pituitary adenoma with intratumoral hemorrhage. Furthermore, a slight increase of α_2 M was noted in many cases of brain tumors treated with ^{60}Co inrradiation and also in cases of chronic subdural hematoma.

In general α_2 M does not pass through the blood-CNS-CSF barrier, and its concentration in CSF is hardly influenced by concentration in plasma. Therefore, an increase of α_2 M in CSF is significant, but a decrease is not always significant.

(8) α_2 HS glycoprotein (α_2 HS)

α_2 HS increased in cases wth ventricular dilation following head injury and ruptured aneurysm. However, cases of glioma and epilepsy did not show any consistent tendency.

(9) haptoglobin (Hp)

Hp combines with hemoglobin in hemolysis, and usually only Hp 1-1 type exists in CSF (Fig. 3). A remarkable increase in Hp was observed in cases of neurinoma and meningitis, but in these cases total protein showed a remarkable increase (Table 5a). A decrease of Hp was observed in cases with recurrent astrocytoma, pinealoma and pituitary adenoma with intratumoral hemorrhage. In all 3 cases of epilepsy, Hp showed a marked decrease. Hp also decreased in cases of head injury and vertebral artery thrombosis.

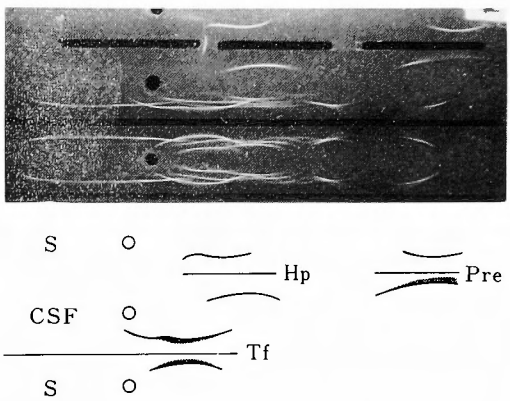

Fig. 3 Immunoelectrophoresis of serum and concentrated CSF (200 x).
CSF in the middle groove shows cathodal elongation of prealbmin and transferrin. Haptoglobin in CSF is type 1-1.

(10) hemopexin (Hx)

Hx is combines with them, but the site where this protein is produced has not yet been elucidated[12]. An increase in Hx was observed in cases of glioma, meningitis and other diseases. In the subacute stage of head injury an increase of Hx was observed, but in cases of chronic subdural hematoma it showed a slight decrease (Table 10). In many cases that Hx increased, a decrease of Hp was observed. However, the concentration of Hx and Hp did not exhibit a reciprocal relationships.

(11) transferrin (Tf)

Tf combines with iron-and other metallic irons, and is said to play a role on the metabolism of metalic irons. Tf increased in cases of astrocytoma, malignant pituitary adenoma, acromegaly, craniopharyngioma, optic neuritis and traumatic cervical syndrome (Table 8). On the other hand Tf decreased in cases of neurinoma, meningitis, multiple sclerosis and NPH. In all these cases, except for multiple sclerosis, an increase of Cp was observed.

(12) β_1C/β_1 A globulin (C3)

Table 10. Change of haptoglobin and hemopexin

	Hp	Hx	
	0.54%	1.16%	control
No. 4	0.70	1.90	ependymoma
No. 5	0.59	2.42	glioblastoma
No. 6	—	1.90	astrocytoma
No. 10	—	1.30	pinealoma
No. 15	—	1.20	pituitary adenoma
No. 19	0.23	1.64	tuberculum sellae meningioma
No. 20	1.88	0.57	acoustic neurinoma
No. 21	3.15	0.70	trigeminal neurinoma
No. 23	—	0.94	epilepsy
No. 24	—	0.85	epilepsy
No. 25	—	1.06	epilepsy
No. 27	—	1.97	hysteria
No. 31	0.44	2.04	gait disturbance
No. 33	—	0.83	chronic subdural hematoma
No. 34	—	2.09	head injury, type III (Araki)
No. 35	0.22	0.61	head injury, type I (Araki)
No. 36	—	4.09	ruptured aneurysm, NPH
No. 37	0.50	2.10	ruptured aneurysm, NPH
No. 39	0.12	1.79	vertebral thrombosis
No. 40	—	0.87	vertebral stenosis
No. 41	0.69	2.19	parkinsonism

C3 increased in cases with glioblastoma, neurinoma and meningitis (Table 11). In almost all cases treated with postoperative ^{60}Co irradiation, a slight increase of C3 was observed. A slight increase was also observed in cases of multiple sclerosis, vertebral arterial stenosis and head injury (type 3). In many cases that concentration of Alb was below 15 mg/dl, C3 showed a decrease. However, since the concentration was too low to be measurable, the influence due to measuring error seemed to be large. Therefore, a decrease in cases of epilepsy might not be significant.

(13) IgA

IgA increased in cases of metastasis, pituitary adenoma with intratumoral hemorrhage, neurinoma and meningitis, while IgA decreased in all 3 cases of epilepsy and in one case of optic neuritis. A slight decrease was observed in cases of chronic subdural hematoma and pituitary adenoma. During infancy and early childhood its concentration was low.

(14) IgG

IgG increased in cases of glioblastoma, ARNOLD-CHIARI malformation and pinealoma. In one case of meningioma IgG in CSF as well as gamma-globulin in plasma showed an increase. IgG also increased in cases of acromegaly, multiple sclerosis and meningitis. On the other hand IgG showed a decrease in cases of intracranial tumors treated with

Table 11. Change of IgA, IgG and C3 component

	IgA	IgG	β_1A(C3)	diagnosis	after cobalt irradiation
	0.83%	12.5%	0.65%	control	
No. 2	1.23	8.3	1.07	medulloblastoma	+
No. 3	1.14(1.01)	11.8(9.6)	0.88(0.84)	third ventricle tumor	+
No. 4	1.19(1.28)	9.8(10.6)	0.70(0.75)	ependymoma	—
No. 5	0.59(0.64)	14.5(15.6)	1.21(1.31)	glioblastoma, cyst +	+
No. 6	—	7.9	0.54	astrocytoma (recurrence)	+(4ys ago)
No. 8	1.42	7.1	0.71	osteoma	—
No. 9	1.58(1.45)	11.7(10.8)	0.99(0.91)	metastasis	+
No. 10	0.81	13.2	0.74	pinealoma	+
No. 14	1.53	12.7	0.87	pituitary adenoma	
No. 16	1.13(1.09)	13.6(13.0)	1.03(0.89)	pituitary adenoma,malignant	
No. 17	0.42	14.3	0.86	acromegaly, diabet. m.	
No. 18	1.13(1.08)	16.2(11.3)	0.58(0.56)	meningioma	
No. 20	1.81	17.7	1.08	acoustic neurinoma, cyst +	
No. 21	1.34(1.46)	12.8(14.0)	1.22(1.39)	trigeminal neurinoma, cyst +	
No. 23	0.28	9.6	0.33	epilepsy	
No. 24	0.76(0.72)	12.1(11.4)	0.45(0.43)	epilepsy	
No. 25	0.44	13.9	0.71	epilepsy	
No. 29	0.44(0.42)	8.6(7.9)	0.83(0.76)	optic neuritis, steroid	
No. 33	0.17(0.20)	9.4(11.1)	0.52(0.61)	chr. subdural hematoma	
No. 34	0.55(0.51)	8.3(7.7)	0.86(0.80)	head inj. type III, steroid	
No. 39	1.01(0.95)	13.9(13.1)	0.74(0.69)	vertebral thrombosis	
No. 40	—	11.9	0.81	vertebral stenosis, child	
No. 41	0.81	15.9	0.58	parkinsonism	
No. 43	0.87	17.9	1.00	multiple sclerosis	
No. 44	2.15(1.91)	16.3(14.4)	1.48(1.31)	menigitis, epilepsy	
No. 46	1.14	19.4	0.52	Arnord-Chiari,	

^{60}Co irradiation.

Besides, in cases of optic neuritis and head injury (type 3) IgG decreased slightly, but these cases had received administration of steroid preparations.

Discussion

1) Methods of measurement

Gottesleben et al.[23] carried out a quantitative determination of proteins in CSF with RID method, and reported that α_1 AG was 0.367 mg/dl, Hp 0.224 mg/dl, IgA 0.226mg/dl, and IgG 1.76 mg/dl. In their determination, however, the fluid was condensed. Thus, the resultant fluid concentrations could not be regarded as really correct values, due to the loss of proteins by the condensation. In the present study, when Pre, α_1 AT and Tf were measured with RID method, the results showed higher values as compared with the results of EID method.

However, RID method is preferable to EID for the measurement of IgG, since the electric

mobility of IgG is equal both in human and rabbit, and the mobility differs according to its types. As IgG was not so low in concentration, the errors of measurement with RID method were small[15)87)], as well as with EID method[92)] A possibility of making errors in EID exists in the difference of the positions of wells on the specific antiserum containing agarose plate and in the difference of the order putting the fluid into wells. In the present study, therefore, the positions of holes applying each sample, i. e. CSF and diluted standard sera, and the order of application, were arranged to be uniform. In many reports on immunological determination, antisera and standard sera are not always uniform[3)]. In the present study, therefore, only Behringwerke products which had undergone the second assay in the medical detartment of Hoechst Japan LTD were used.

2) Mean values of control group

TOUTELLOTTE et al. estimated the concentration of Alb in CSF to be below 30 mg/dl as normal range[90)]. However, concerning protein concentrations in CSF of normal subjects, only IgA and IgG, have been reported. Therefore, the data reported by BOCK in Sweden and by SCHULLER in France, which were estimated in patients with neurological disorders, were compared with those obtained in the present study (Table 3). In BOCK's report the mean value of the indivisual proteins in CSF in 22 neurologically abnormal patients proved to be almost normal, if the cases with abnormalities of serum proteins and with liver and kidney diseases were excluded. In consideration of the concentration of each protein, racial differences have to be considered. According to GIRARD[21)], the difference of plasma protein concentrations between Caucasians and Africans are very great, e.g. Africans have IgG in approx. 3 times higher concentration, and each protein in CSF of Africans shows a considerable difference from that of Caucasians. The difference of plasma protein concentrations between Japanese and Caucasians are comparatively small, so that the diffference of protein concentrations in CSF is considered to be negligible.[19)49)77)95)] Table 3 shows the mean values of measurable plasma in CSF. When unmeasurable cases were regarded as 0 mg/dl, the values shown in the parentheses are close to the normal values. Comparison of these concentrations of CSF with those reported by BOCK revealed that the values of Pre and α_1 AG were lower, while those of IgA and IgG were higher in Japanese, as comared with those of Caucasians. Therefore, the data on Japanese are resemble closely with those of Bock, if plasma protein concentrations are taken into account.

3) Analysis of plasma proteins in CSF, especially correlation between albumin and individual proteins

In most of the previous reports on protein concentrations in CSF, change in total protein has not been considered, but their measured values of IgG were compared with the standard values and total protein in CSF in case of multiple sclerosis and other diseases [46)91)]. Although it is very rare that proteins in plasma increase more than twice, proteins in CSF sometimes increase many times, and in morbid states the majority of proteins show high concentrations. Therefore, a mere comparison of measured concentrations of individual proteins in CSF seems not to be significant. For the purpose of examining the relative

changes in individual proteins in CSF the following methods should be considered : 1) comparison of individual proteins with total protein in CSF, 2) comparison of it with total plasma protein in CSF, and 3) comparison of it with Alb in CSF. Approximately 30% of total protein in CSF consists of lipoprotein, fibrinogen and some specific CSF proteins. Alb and total protein in CSF are generally believed to be proportional, but what is represented as the total protein in CSF is not clear. Therefore, a comparison of a protein with total protein is not reasonable. Thus, as stated by TOURTELLOTTE, a comparison of a protein with Alb in CSF may be more appropriate. However, since Alb in CSF is subjected to the changes of Alb in plasma, we must be careful in interpretation. In such a case changes of Alb in CSF may be estimated by comparison with total plasma protein in CSF. However, if little changes in concentration of Alb in the plasma are present the difference between these two methods in minimal, for Alb in CSF occupies approx. 1/2 of total protein derived from plasma. In the present study all cases with increased Alb in CSF showed parallel increase of plasma Alb concentration except two cases. Only in the latter cases, a comparison was made between Alb and total protein in the plasma. As recently reported by GANROT[18], such as estimation on the rate of concentration of individual proteins in CSF from that in plasma seems to be more appropriate.

§ Correlation between albumin and individual proteins

Since quantitative determination of all proteins in CSF is ordinarily impossible, a comparison of a protein with Alb is believed to be the best method. However, some proteins which show drastic diurnal variations, such as Hp, Cp and α_2 M[6], can not be correlated with Alb. An increase in these proteins often indicates an acceleration of the permeability of the blood-CNS-CSF barrier[8][9]. As shown in Table 4, α_1 AG, α_1 AT, Tf and IgG have high correlations with Alb at normal fluid concentrations. The regression lines between Alb and indivisual proteins except Pre pass near the origin, which is understood from the value of "a". For instance, a relation between α_1 AT and Alb is denoted by a formula $Y=a+bX$. Since the value of "a" is near the origin, the ratio of the two proteins in CSF is considered to be equal to approximately $b=0.063$ (Fig. 2). The product "b" and the concentration of Alb in plasma is useful for judging whether its concentration in CSF is relatively higher or lower than that in the plasma. For example, α_1 AG corresponds to "b" $\times$ 4100mg/dl=72mg/dl and α_1 AT corresponds to "b" $\times$ 4100mg/dl=253mg/dl. Comparing these results with the mean value of plasma proteins of Japanese shown in Table 3, little difference is noted in α_1 AG and α_1 AT. On the other hand C3 showed the value of 40mg/dl, IgA 60mg/dl and IgG 800mg/dl, which constitutes 30 to 60% of plasma protein concentrations. In a similar way concentrations of Cp, α_2 M and Hp in CSF were compared with those of Alb, and proved to be considerably lower than that in the plasma, while Hx and Tf corresponded to 80mg/dl and 400mg/dl in the plasma respectively. Thus it may be considered that the concentration of these two proteins are relatively higher in CSF. These phenomenon indicate that protein concentration in CSF is proportional to plasma protein concentration, and inversely to molecular weights of plasma

protein[71]. But there are some exceptions ; Pre exists in high concentration in CSF. Tf type 2, so-called τ fraction, has been reported to be observed only in adults[36)39)]. Hx existed in slightly higher concentration than in other reports. It has been pointed out that many Caucasians have Hx in the plasma with molecular weight, 80,000 (type 2), while many Japanese have its complex body (type 1) with high molecular weights[52]. Since proteins with larger molecular weights are difficult to diffuse, a complex body with apparently large molecular weight shows low concentration with RID method. The mean concentration of Hx in the plasma in Japanese is 50mg/dl[86]. If Hx in the plasma in Japanese consists of Hx (type 2), the concentration might correspond to 80 to 100mg/dl, according to HIRAYAMA's report[29]. However Hx in CSF consists of type 2. Thus, such a difference in plasma between Caucasians and Japanese may be due to the difference of molecular weight of Hx. In the present study Hx concentration in CSF was a little higher than that of Caucasians.

Hp in CSF also corresponds to a half of the concentration in plasma, but according to BOCK, approximately 1/5 of the concentration in plasma. It has been reported that Hp in CSF is ordinarily only Hp type 1-1 which is a smaller molecular weight, and that if the blood-CNS-CSF barrier is destroyed, types 2-1 and 2-2 with larger molecular weights might appear in CSF from the plasma (Fig. 3). In the present study concentrations of Hp in CSF were very low and unmeasurable in half of the cases. Hp in the plasma of Japanese consists of 53% of type 2-2, 45% of type 2-1 and 4 to 5% of type 1-1. On the other hand in Caucasians more than 75% of Hp is type 1-1[77]. Since the type 1-1 with smaller molecular weights shown apparently about 1.5 to 2.5 times higher values with RID method, a correction in each type of Hp[44] is necessary.[59] Therefore, there seems to be no difference of plasma Hp concentrations between Japanese and Caucasians. From these point of view there seems to be no difference between the values of our control group and these reported by BOCK. However, it must be noted that since Hp is a protein with drastic diurnal variations, it easily decomposes during the preservation.

4) Analyses of indivisual proteins in each case

(1) albumin (Alb)

Normal concentration of Alb in CSF is below 30mg/dl. In the present study Alb was below 30mg/dl in 43 cases, and 30 to 60mg/dl in 5 cases. The total of 14 proteins occupied approximately 60% of total CSF protein. The changes of concentrations of these 14 proteins in CSF may be due to the following factors :

1. Change of the ratio of concentration of the plasma Alb 2. Intracranial hemorrhage 3. Increase of the permeability of the blood-CNS-CSF barrier due to inflammation or intracranial tumor 4. Cyst formation communicating with the CSF-space 5. Changes of the plasma protein concentrations, etc.

Among these factors, it has been generally accepted that the percentage of Alb concentration in CSF varies in proportion to those in plasma[72]. Concentration of each protein was corrected on the basis of the ratio of Alb to total protein in plasma. However, it was not easy to decide whether the protein in question increased or decreased specifically in

cases that its corrected value was close to the control. As shown in Table 6, in cases of intracranial tumor in which their total protein in CSF showed an increase over 30mg/dl, the CSF fractions showed a tendency toward the plasma fractions. On the other hand in cases that Alb was below 30mg/dl, change of concentration of each protein was little, especially in pituitary adenoma. But in cases of ruptured aneurysm and epilepsy, change in Hp or IgA was remarkable, probably due to hemorrhage or drug administration.

(2) preadlbumin (Pre)

It has been observed that Pre in CSF shows high concentration, and that concentration of CSF in the ventricle is higher than in the lumbar subarachnoid fluid.[83] This protein is said to have an activity of transporting Vitamin A and thyroid hormone in the plasma by combining with them. An increase of Pre was observed only in cases of hydrocephalus. According to TAKASE[82], a relative increase of Pre occurs in an atrophy or degenerative disease of the brain. This may be due to inhibition of the transport of Pre from the CSF to the blood vessels. In cases of communicating hydrocephalus and NPH, absorption of the CSF through the arachnoid villi is disturbed. Remarkable increase of monoamine in cases of communicating hydrocephalus might reflect disturbance of the mediated transport from the brain to the endothelium capillaries[99]. The increase of Pre in CSF in communicating hydrocephalus may be explained by the same mechanism.

(3) α_1 acidglycoprotein (α_1 AG)

It is believed that α_1 AG increases after operation and in meningitis.[2] If brain tumor is regarded as a kind of chronic inflamatory process, as DELANK et al. mentioned,[10] there may be cases which α_1 AG increase in plasma. In 5 cases of pituitary adenoma only 1 showed an increase, in which several biochemical abnormalities such as LDH, RA, etc. were discovered in hematological tests. In tumor groups, especially in cases with metastatic brain tumors, much more increase of α_1 AG was observed than in other disease groups. WEBER[94] reported on cases of metastasis of gastric cancer to the brain with a remarkable increase of α_1 globulin in CSF, which is considered due to the increase of α_1 AG. There are few reports on a remarkable increase in α_1 AG in CSF in cases of metastatic brain tumor.

(4) α_1 antitrypsin (α_1 AT)

α_1 AT, α_1 X and α_2 M as well as inter-α-trypsin inhibitor, antithrombin and Cls-inhibitor act as proteinase inhibitors.[27] α_1 AT acts especially on elastase, trypsin, chymotrypsin, plasmin and kallikrein, for defense of inflammatory reactions.[76] It has been reported that in some cases of cancer an increase of α_1 AT in the plasma was found.[84] An increase in α_1 AT in CSF is considered to reflect the increase in α_1 AT in plasma.[96] In cases of pituitary adenoma, a decrease in α_1 AT was observed. This may be due to minimal destruction of the brain. However, further studies are necessary in regard to the mechanism of decrease of α_1 AT.

(5) α_1 antichymotrypsin (α_1 X)

A very high correlation of this protein to α_1 AT in CSF was observed. A remarkable

increase in α_1 X was noted only in cases with metastasis and malignant pituitary adenoma. Furthermore, in cases with malignant brain tumor there was an increase of α_1 X in the plasma and in the cyst.[84] It might be concluded that α_1 X relates with the malignancy of tumor.

(6) ceruloplasmin (Cp)

Since the molecular weight of Cp is as large as 160,000, Cp shows a relatively lower concentration in the normal CSF than in the plasma. In cases of malignant pituitary adenoma and metastasis, an increase of Cp was demonstrated, which is probably related destruction of the barrier, and to the blast formation of a tumor, for Cp has an oxidase-activating property. There were many cases where Cp decreased. In these cases a possibility of the activation of histamine or an abnormality in copper metabolism cannot be denied.[74]

(7) α_2 macroglobulin (α_2 M)

The molecular weight of this protein is as large as 820,000, and it has been said that α_2 M does not exist in the normal CSF. WEBER reported that in cases of pituitary adenoma with an increase of total protein, there was an increase of α_2-globulin fraction which might be either α_2 M or Hp.

(8) α_2 HS glycoprotein (α_2 HS)

The concentration of α_2 HS is influenced by many unknown factors. Further studies are required.

(9) haptoglobin (Hp)

Hp in CSF consists of the type 1-1 with the small molecular weight[4]. Therefore, the concentration of Hp in CSF is a little lower than Hp in plasma which contains type 2-2 in addition to type 1-1. In cases of meningitis[53], and neurinoma, there is an increase in Hp in CSF On the other hand, in cases with hemolysis, Hp combines with hemoglobin[31], so that Hp is consumed and decreases, as seen in cases of head injury and ruptured aneurysm. Moreover, when Vitamin C is administered or patients are children, the concentration of Hp in plasma is low[86].

(10) hemopexin (Hx)

Hx is also consumed in hemolysis. In cases of head injury an increase in Hx was observed at the convalescent stage.[40,42] Therefore, the measurement of Hx in CSF may be useful for the estimation of the stage of head injury.

(11) transferrin (Tf)

Tf combines with iron, copper, zinc, gallium and indium in the plasma. Tf has an abactericidal activity on gram-negative bacilli[24,73]. Tf in the plasma is said to increase in case of anemia[75] In one of the cases of head injury (type 3), which associated with pelvic fracture and severe anemia, there was an increase of Tf in CSF. In cases of craniopharyngioma with an increase of Tf in CSF there was a remarkable increase of β-globulin fraction in plasma which indicated an increase in Tf. WEBER, also reported that a remarkable increase in β-globulin fraction in CSF was observed in cases of benign

intracranial hypertension, which might be related with estrogen[64]. There are two types of Tf Type 1 & Type 2[7]. Type 1 is contained both in CSF and in plasma, and Type 2 is observed only in CSF. However, both types of Tf are immunologically the same and linked together, showing the two-peaked W-shape at immuno-electrophoresis (Fig. 3).

Although it has not yet been clarified whether Tf type 2 is produced in the brain or not, Tf type 2 is believed to be deprived 4 molecules of sialic acid from one molexcule of Tf type 1 by neuraminidase.[54][61] According to KOLAR[39], Tf type 2 in CSF increases with age, and also in ischemic lesions. In the past study Tf type 2 increased remarkably in immunoelectrophoresis of the cystic fluid in cases of metastasis from frontal sinals cancer, lung cancer and glioblastoma.[84] Kawakita pointed out that Tf type 2 is contained higher in concentration in the ventricular fluid than in the lumber subarachnoid liquid. However, since there is no definite correlation between Tf type 1 and Tf type 2[39], it cannot always be said that Tf in CSF shows an increase in ischemic lesions in the brain. The concentration of Tf in CSF is sometimes the sum of type 1 and type 2. In cases of meningitis and neurinoma, Tf showed a decrease. In these cases a relative decrease in Tf type 2 was found. Therefore, it is necessary to examine both types simultaneously.[17]

(12) β_1C/β_1A globulin (C3)

β_1C is decomposed into complements C3a and C3b, and in turn C3b into C3c (=β_1A) and C3d (=α_2D). C3 protein paticipates in cell-lysing action, histamine isolation, chemotaxis of leucocytes, and acceleration of coagulation due to immunocomplex.[86] Few reports have been made on β_1C/β_1A globulin in CSF. In PROPPE's report,[63] the normal value of this protein in CSF is 0.413mg/dl. This value is considerably higher than that shown in Table 3. Since β_1 C is decomposed during preservation and its molecular weight becomes smaller,[97] particular caution must be taken. In the present study an increase of C3 was found in cases of tumor, especially malignant tumor.

(13) IgA

IgA increased in cases of intracranial tumor and meningitis. When the blood-CNS-CSF barrier is destroyed, IgA always increases. TAKASE[81] reported that an increase in IgA was observed in cases with vascular ischemia and diabetic neuropathy. On the other hand, since plasma IgA in infants is low in concentration, their IgA in CSF is naturally low. A decrease in IgA was observed in cases of epilepsy, which had been treated with hydantoin. A decrease of plasma IgA may be due to administration of hydantoin or to convulsion.[25][78] At any rate the measurement of IgA in CSF is useful for the management of epilepsy.

(14) IgG

IgG exists in the second highest concentration in CSF next to Alb, and is produced in great quantities in the brain in cases of subacute sclerosing panencephalitis (SSPE) and multiple sclerosis.[16][22][37][38] Among the cases of intracranial tumor, pituitary adenoma did not show its increase, while the tumor with a cystic component, such as glioma, neurinoma etc. showed its increase. Meningitis, parkinsonism and multiple sclerosis

showed its increase.[60)100)] In one case of menigioma, there was an increase of IgG both in plasma and in CSF. In cases of acromegaly, the catabolism of IgG and Alb is accelerated, but the production of IgG is much more accelerated than Alb.[62)] Consequently IgG in CSF increases. Gamma-globulin is reported to increase in CSF 3 to 6 weeks after operation.[1)] However, if ^{60}Co irradiation or steroid preparation were given, IgG shows a decrease even after operations. NELLHAUS[56)] pointed out IgG decrease in infants. This is due to the low concentration of IgG in plasma.[28)57)] There are several factors which cause an increase of IgG in CSF. These are: 1) an increase of IgG in plasma, 2) an acceleration of permeability of blood-CNS-CSF barrier, 3) a hemorrhage into the subarachnoid space, 4) a specific IgG production, etc.

GARDNER reported that a remarkable increase in gamma-globulin in the plasma and cystic fluid was noted in cases of craniopharyngioma and acoustic neruinoma.[20)] Saint-Paul reported that α_2 M and IgG showed high concentrations even in a long preserved blood.[65)] An increase of IgG, in cases of malignant tumor and meningitis seems to be due to an acceleration of the permeability of blood-CNS-CSF or blood-tumor barrier.[53)] A slight increase of IgG was observed in subarachnoid hemorrhage, while increase of α_2 M and other proteins with large molecular weights was remarkable. In the case of chronic subdural hematoma, however, IgG showed a decrease, because of a relative increase in Alb probably due to edema in the brain. There are a few reports that IgG was produced specifically in cases of plasmacytoma and microglioma.[44)94)] In the other study K-L ratio of IgG was examined in 40 cases of primary brain tumor, and the abnormality of the ratio was found in 4 of 5 cases of pinealoma.[84)] Therefore, there is a possibility that some kinds of abnormality of immunoglobulin may exist in pinealoma.[45)51)] If so, lymphocytes found in pinealoma may play a role.[41)] Weber reported that an increase of α_2-globulin fraction and gamma globullin in CSF was found in patients with pinealoma associated with necrosis following irradiation of 12,500 rad. In the present study, however, an increase in IgG was not observed in cases of intracranial tumor irradiated 5,000 rads postoperatively. Since there was a decrease of Pre in these cases, there is a possibility that proteins with large molecular weights appeared in the extracellular spaces in the tumor by irradiation.

conclusion

The results of analysis of the 14 plasma proteins in CSF indicate that the changes of the individual proteins in CSF reflects the dynamic aspect of the various intracranial pathology. Therefore, correlative study of the individual proteins in CSF may be useful for management of intracranial diseases. There are several factors which influence on the changes of the proteins in CSF, such as abnormalities of the plasma proteins, ages and races, etc. The proteins in CSF play a great role in the metabolism of the brain tissue. Therefore it is important to study a specific action of indivisual proteins in CNS. For this purpose, repeated measurements of proteins both in plasma and CSF are essential.

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和文抄録

髄液中の14種類の血漿蛋白の定量と臨床分析

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1. 日本人における髄液中の血漿蛋白・14種の定量を行った。

2. control 群において，髄液中では，albumin と，haptoglobin 以外の他の血漿蛋白との間には，一定の相関が認められた．

3. control 群においては，髄液の血漿蛋白の濃度は，血漿中の濃度と比例し，かつ，分子量15万以上の蛋白では，分子量の大きさに反比例する傾向を認めた．ただし，prealbumin, transferrin は，血漿以外にも由来している可能性は否定できなかった．

4. 血漿に由来する蛋白を分析するには，これらの蛋白の総量，または，albumin との濃度比により，検討することが必要である．

この方法により，各蛋白について，各症例において，比較，検討した．その結果，

a) prealbumin は hydrocephalus で増加し，脳の代謝と，特に関係があると考えられる．

b) 手術，放射線照射，ステロイド剤の投与，肝障害などがあると，髄液蛋白に，大きな変動がみられ，これらは，血漿蛋白の変動をよく反映していると考えられた．

c) α_1 antitrypsin, α_1 acidglycoporotein, α_1 antichymotrypsin の増加が head injury, meningitis, intracranial bleeding, 一部の brain tumor において認められた．

d) とくに，悪性の脳腫瘍では $\alpha_1$antichymotrypsin, ceruloplasmin の増加傾向がみられた．

e) intracranial bleeding があると，haptoglobin は著明に減少していた．この場合，hemopexin の増減は，予後と関係していると考えられた．

f) epilepsy では，IgA, haptoglobin が著明に減少していた．

g) IgA の増加は，blood-CNS-CSF barrier の透過性の亢進をよく反映するものと考えられる．

h) cyst の存する脳腫瘍，とくに neurinoma, glioblastoma では，分子量の大きい蛋白，とくに α_2 macroglobulin, β_1C β_1A globulin (C_3), IgG, IgA の増加がみられた．